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The Myeloid differentiation primary response 88 expression in central nervous system lymphomas

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ABSTRACT

Aims: A prominent adaptor protein that signals from many receptors called myeloid differentiation primary response 88 (MYD88) coded by MYD88 gene was evaluated. Our aim was to record the level of MYD88 expression and its relation with clinicopathological parameters in both primary and secondary central nervous system (CNS) lymphomas.

Methods: MYD88 protein expression was analyzed by two different classification using immunohistochemistry in ten patients who were diagnosed in our hospital. The samples that were collected from patients before treatment were evaluated and specified by a hematopathologist. Demographic and clinical information of the patients were obtained from hospital database and files. The primary outcome was the presence and prevalence of MYD88 expression. Secondary outcomes were determined as the evaluation of the relationship between MYD88 expression and disease prognosis.

Results: MYD88 protein expression was examined in 10 in patients of which 9/10 cases (90%) expressed the protein in wide ranges of intensity and density. Six patients (60%) expressed high-level of MYD88 protein where as one patient did not, and three patients expressed low quantity of MYD88 protein that deceased after diagnosis. Most CNS lymphoma patients had an activated B cell-like immunophenotype.

Conclusion: Primary and secondary CNS lymphomas showed expression of MYD88 protein without regards of lymphoma subtype.

Keywords: Central nervous system lymphoma, immunohistochemistry, MYD88

INTRODUCTION

A rare extra-nodal non-Hodgkin lymphoma is primary central nervous system diffuse large B-cell lymphoma (PCNS DLBCL) that primarily arises in the brain, spinal cord, leptomeninges, and vitreoretinal compartment of the eye. The term is interchangeable with primary central nervous system lymphoma (PCNSL). Rarely, other types of lymphomas can be seen in the central nervous system (CNS), the familiarity with these conditions will help in recognizing and further differentiating to establish a diagnosis.[1] Secondary CNS lymphoma (SCNSL) initially arises from another area of the body and spreads to the CNS (in contrast to primary CNS lymphoma). It may be an isolated recurrence or a part of a systemic disease at the time of presentation but usually it is a non-Hodgkin lymphoma. Myeloid differentiation primary response 88 (MYD88) coded by MYD88 gene is a prominent adaptor protein that signals from many receptors.[2]

Development of immune responses includes MYD88. The binding of ligands to different toll-like receptors or interleukin (IL)-1/IL-18 receptors induces the association of MYD88 with the Toll/IL1R domain of these receptors, resulting in the activation of the NF-κB signaling pathways in immune cells.[3] MYD88 increases IL-6 and IL-10 secretion and also promotes the secretion of interferon-β activates leading to the activation of JAK-STAT3 signaling. Interferon-β is a cytokine that has immunosuppressive effects that causes tumor cells to escape immune surveillance. STAT3 interacts physically with NF-κB heterodimers and transactivates NF-κB target genes.[4] It is recurrent in systemic DLBCL (10–20%), but more so in PCNSL (≥50%).[5,6] Bruton tyrosine kinase (BTK) integrates B-cell antigen receptor (BCR) and toll-like receptor signaling and cell survival in various B cell lymphomas.[7] Ibrutinib, a first-in-class oral inhibitor of BTK was used to show BTK being involved in oncogenic BCR signaling that controls the survival of a human activated B cell (ABC)-like subtype of DLBCL.[8]

CNSL treatment is comprised of chemotherapy and/or radiotherapy (RT) consolidated with an autologous stem-cell transplantation in eligible patients.[9] The emergence of new therapies designed for molecular targets, such as MYD88 signaling pathway, may offer alternative treatment options for patients diagnosed with these rare tumors.[10]

In this study, we aimed to retrospectively test formalin-fixed paraffin-embedded (FFPE) tissue samples obtained from

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CNS tumors for the expression of MYD88 protein and their relationship with clinical and pathological variables in CNS lymphomas.

METHODS

The study was conducted with the permission of İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 23.06.2021, Decision No: 02-2988). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

MYD88 protein expression was analyzed by two different classification using immunohistochemistry (IHC) in ten patients whom were diagnosed in our hospital between 2014-2020. The samples that were collected from patients before treatment were evaluated and specified by a hematopathologist. Demographic and clinical information of the patients were obtained from hospital database and patient files. IHC staining and evaluation.

Four categories were classified according to the staining intensity on a scale from 0 to 3 as follows: 0, no reaction; 1, weak reaction; 2, moderate reaction; and 3, strong reaction. In this article we identified it as first classification model.

Three categories were classified according to the widespread of staining scored as 0 (0% of tumor area stained), 1 (< 10%), 2 (10–50%), or 3 (> 50%) (**Figure**).[2] We identified it as second classification model. Staining intensity and the percentage of tumor cell positivity were evaluated and recorded by a hematopathologist.

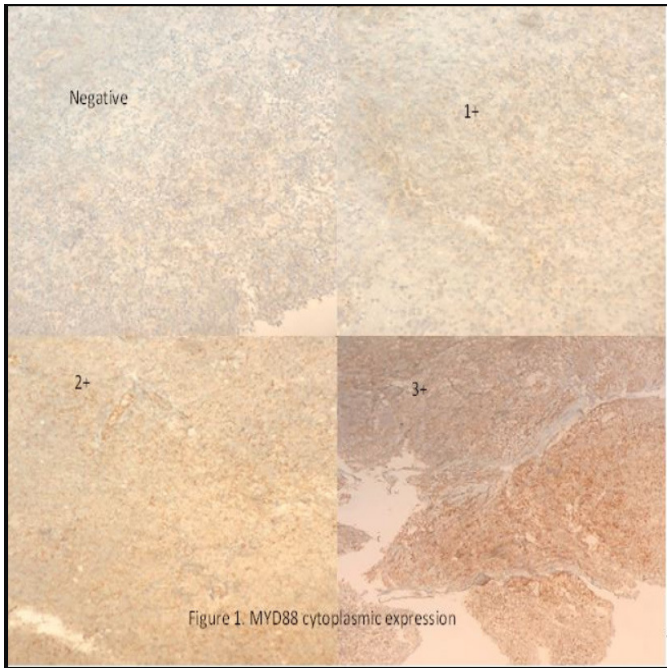

Figure. Scoring system of MYD88 expression

MYD88 protein expression in CNS lymphomas. All cases are semi-quantified in terms of intensity of MYD88 staining as score 0 (A), score 1 (B), score 2 (C), and score 3.

We also checked for the presence of Bcl-2, Bcl-6, c-Myc, MUM-1, CD10, CD20, Ki 67 and EBER with IHC. Descriptive statistics were used to define frequencies of categorical variables and mean or median (std. deviation or range) to analyze numerical variables. SPSS 17.0 were used to analyze the data.

RESULTS

A total of 10 patients; 4 females and 6 males were diagnosed between 2014-2020 were included in the study. Median age was 56.2 and 4 patients were over 65 years. Eight of them were diagnosed with DLBCL-ABC-like phenotype, 1 of them was marginal zone lymphoma and the last one was follicular lymphoma grade 3a.

Two of the patients had relapsed/refractory disease, the others were newly diagnosed. Five patients were not evaluated for lactate dehydrogenase (LDH) levels. One patient's LDH level was very high (700 U/L), 3 of them were over the laboratory reference limits, 1 was at a normal range at the time of the diagnose. Median ki67 of all cohort was 80% (10-95). Only 2 patients had B symptoms. All of the patients had neurological symptoms such as sight loss, paresthesia, hemiparesis, deafness, nystagmus, ataxia, hemiplegia, dysarthria, facial paralysis, parkinsonian symptoms and paraplegia. Cerebrospinal fluid (CSF) of only 3 patients was evaluated and involvement was detected in one. Two patients had 3, 2 had 1 and others had 2 as an Eastern cooperative oncology group (ECOG) performance status score. Disease involvement were unifocal at 4 patients and multifocal at 6 patients. Three patients were lost to follow up before treatment plan. The number of patients matching the initial treatment after the diagnosis of PCNSL or SCNSL were as follows; 2 - R-CHOP+high dose methotrexate (MTX), 1 - mini-R-CHOP+RT, 1 - De-Angelis protocol, 1 - Matrix protocol, 1–ibrutinib+nivolumab and 1 was lost before the initiation of treatment. One patient was able to proceed with autologous stem cell transplantation. The outcomes achieved with aforementioned treatment approaches are summarized at **Table 1**. MYD88 protein expression was examined in 10 in patients of which 9/10 cases (90%) expressed the protein in wide ranges of intensity and density. Six patients (60%) expressed high-level of MYD88 protein where as one patient did not, and three patients (patient 2,3,9) expressed low quantity of MYD88 protein that deceased after diagnosis. In our study most patients had ABC-like immunophenotype (8/10). Median expression of MYD88 was calculated as 95 (20-100) according to second classification (**Table 2**).

Five patients were diagnosed with supratentorial brain biopsy, 3 patients with spinal mass biopsy and 2 patients with cerebellum biopsy.

Bcl-2 was positive in 7 of 8 patients (87.5%). Bcl-6 was positive 9/10 patients (90%). C-myc was evaluated in 6 patients and 3 of them were positive (50%). Eight patients showed MUM-1 positivity. CD 10 expressions were present in 3/10 and CD 20 was 9/10. Patient that did not express CD20 expressed PAX5 and CD79a. There weren't EBER positivity in all who were examined.

DISCUSSION

Most patients in our study had ABC-like immunophenotype, that has been previously reported.[11] We analyzed MYD88 protein expression by IHC analysis in CNS lymphomas, median value of the expression level was 69%. It was present in both primary and secondary CNS lymphomas, only one patient lacked to show expression of MYD88 who was diagnosed with a PCNSL. MYD88 positivity was present 4/5 in primary CNS lymphoma and 4/4 in secondary CNS lymphoma. It is recurrent in systemic DLBCL (10–20%), but more so in PCNSL (≥50%).[5,6]

Table 1. Characteristics of patients with central nervous system lymphoma

Patient	1	2	3	4	5	6	7	8	9	10
Initial diagnosis	DLBCL-ABC	Marginal zone lymphoma	DLBCL-ABC	DLBCL-ABC	Follicular lymphoma -3a	DLBCL-ABC	DLBCL-ABC	DLBCL-ABC	DLBCL-ABC	DLBCL-ABC
Age	52	80	27	34	66	43	73	46	77	64
Gender	Female	Male	Male	Male	Female	Male	Female	Male	Male	Female
Newly diagnosed/ R/R Disease	Newly diagnosed	Newly diagnosed	Newly diagnosed	Newly diagnosed	Newly diagnosed	Newly diagnosed	R/R Disease	Newly diagnosed	Newly diagnosed	R/R Disease
Diagnosed from	Temporal lobe	Spinal epidural mass	Cerebellum	Foramen Luschka mass	Epidural mass	Parietal lobe	Temporal lobe	Cerebellum	Occipital lobe	Spinal epidural mass
Diagnosis time	26.06.2019	01.08.2019	24.02.2014	29.02.2016	13.09.2019	23.02.2017	02.02.2018	31.01.2020	24.11.2015	21.10.2020
LDH	295	Unknown	231	Unknown	Unknown	Unknown	390	176	Unknown	705
B symptoms	-	-	-	-	-	-	-	+	-	+
Neurological Symptoms	Sight loss	Paresthesia	Hemiparesis	Deafness Nistagmus Ataxia	Hemiparesis	Hemiparesis	Hemiplegia dysarthria	Facial paralysis	Parkinsonian symptoms	Paraplegia
CSF involvement	Unknown	Unknown	None	Unknown	None	Unknown	Unknown	+	Unknown	Unknown
ECOG	1	2	1	2	2	2	3	2	2	3
Multifocal/unifocal involvement	Unifocal	Unifocal	Multifocal	Unifocal	Multifocal	Unifocal	Multifocal	Multifocal	Multifocal	Multifocal
Primary/secondary CNS lymphoma	Primary	Patient was lost before evoluation	Primary	Primary	Secondary	Primary	Secondary	Secondary	Primary	Secondary
Treatment	Rtx+mtx+alxn		De Angelis	Unknown	R-CHOP+high dose mtx	Unknown	R-miniCHOP+RT	R-CHOP+high dose mtx	Unknown	Ibrutinib+ nivolumab
Autologus transplantation	+		-	Unknown	-	Unknown	-	-	Unknown	-
Treatment response	Complete Remission		Unknown	Unknown	Complete Remission	Unknown	Not achieved a response	Not achieved a response	Unknown	Not achieved a response
Last Seen on	01.04.2021		19.05.2014	01.03.2016	03.02.2021	06.03.2017	10.04.2018	25.04.2020	24.02.2016	29.11.2020
Alive/ex	Alive	Ex	Unknown	Alive	Alive	Unknown	Ex	Ex	Ex	Ex
Overall survival	646	10	85	2	510	12	69	86	93	42

LDH: Laktat dehidrogenaz, ECOG: Eastern cooperative oncology group, CNS: Central nervous system, MTX: Methotrexate, CSF: Cerebrospinal fluid

Table 2. Pathological features in patients with central nervous system lymphoma

Patient	MYD 88 first cl.	MYD 88 second cl.	Pathology	Localization	Type of lymphoma	Bcl-2	Bcl-6	C-Myc	Mum1	Cd10	Cd20	Ki 67	EBER
1	3+	90% (3)	DLBCL-ABC	Temporal lobe	Primary CNS lymphoma	+	-	-	-	-	+	40%	-
2	1+	20% (2)	Extranodal marginal zone lymphoma	Spinal mass	Patient was lost before evoluation	+	+			+	+	10%	-
3	1+	30% (2)	DLBCL-ABC	Cerebellum	Primary CNS lymphoma		+		+	-	+	80%	
4	-	-	DLBCL-ABC	Foramen Luschka mass	Primary CNS lymphoma		+		+	+	+	90%	-
5	2+	100% (3)	Follicular lymphoma grade 3a	Spinal epidural mass	Secondary CNS lymphoma	+	+	-	+	+	+	50%	
6	3+	95% (3)	DLBCL-ABC	Parietal lobe	Primary CNS lymphoma	+	+	+	+	-	+	95%	-
7	1+	100% (3)	DLBCL-ABC	Temporal lobe	Secondary CNS lymphoma	+	+	-	+	-	+	70%	-
8	3+	100% (3)	DLBCL-ABC	Cerebellum	Secondary CNS lymphoma	+	+	+	+	-	+	95%	-
9	1+	40% (2)	DLBCL-ABC	Occipital lobe	Primary CNS lymphoma	-	+		+	-	+	90%	-
10	2+	100% (3)	DLBCL-ABC	Spinal mass	Secondary CNS lymphoma	+	+	+	+	-	-	80%	-

MYD 88: Myeloid differentiation primary response 88, CNS: Central nervous system

Choi et al.[12] had examined MYD88 expression with IHC analysis in DLBCL. The results of their scoring models assessed the level of MYD88 expression. The result did not correlate between protein over-expression and clinical parameters.[12] In our study there were no significant difference between MYD88 expression and age. But our cohort was not quantitatively enough to reach statistical significance.

Caner et al.[8] determined the prevalence of MYD88 L265P mutation and the level of MYD88 expression. Consecutively they also compared their results to clinical and pathological parameters in mature B-cell NHLs. They revealed no correlation between protein over-expression and clinical parameters or a positive correlation between MYD88 mutation and expression. However they were able to document a strong positive correlation between L265P mutation and protein over-expression. Their results showed high levels of MYD88 were associated with older age and poor prognosis. Therefore, they hypothesized that MYD88 over-expression together with L265P mutation could be used as a prognostic marker. MYD88 over-expression without mutation didn't predict the prognosis of the disease.[13]

Three patients were deceased before treatment plan was initiated. Two patients were under R-CHOP chemotherapy regimen, 1 was mini-R-CHOP+RT, 1 was De-Angelis, 1 was Matrix , 1 was ibrutinib + nivolumab and 1 was exitus before the evaluation. One patient was able to achive autologous transplantation.

Prior therapies were given to five patients, 2 of them including MTX chemotherapy, 1 RT, and 1 autologous hematopoietic cell transplantation. Since our study was a retrospective study, we saw that most of the patients received MTX-based chemotherapy. The 64 year old patient that had relapsed disease and co-morbidities using 560 mg ibrutinib and nivolumab daily, died after 42 days due to fragility.

Limitations

The biggest limitations of our study were the small number of patients and the single-center experience.

CONCLUSION

Primary and secondary CNS lymphomas showed expression of MYD88 protein without regards of lymphoma subtype. Further investigations on a larger scale using homogeneous population with longer period of follow-up is required to aid the assessment of MYD88 protein role on the prognosis and treatment of CNS lymphomas. NF-κB pathway directed agents like ibrutinib and lenalidomide, understanding of MYD88's up-regulation mechanism's other than mutation and also its clinical implications. Up to our knowledge, this study is the first to document the presence of MYD88 expression on a Turkish CNS lymphoma patient group.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 23.06.2021, Decision No: 02-2988).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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